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PATENTS

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s):	Akira Suyama, et al.	**Examiner:**	Arun K. Chakrabarti
Serial No:	09/872,881	**Art Unit:**	1634
Filed:	June 1, 2001	**Docket:**	14683
For:	METHOD OF DETECTING NUCLEIC ACID	**Dated:**	October 21, 2002

Assistant Commissioner for Patents
United States Patent and Trademark Office
Washington, D.C. 20231

RESPONSE UNDER 37 C.F.R. §1.121

Sir:

In response to the Official Action dated April 19, 2002 and in accordance with the provisions under 37 C.F.R. §1.121, Applicants submit the following amendment for entry in the above-identified case.

IN THE CLAIMS:

Please amend claims 1, 2, 8-15 as follows:

CERTIFICATE OF MAILING UNDER 37 C.F.R. § 1.8(a)

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Dated: October 21, 2002

Debby Gerber

1.(Amended) A method of detecting or quantifying a target nucleic acid having a predetermined sequence in a specimen comprising:

(a) preparing a probe A and a probe B, said probe A being a first probe which has a sequence F' complementary to a first partial sequence F of the target nucleic acid and a binding molecule bound to the sequence F', and

said probe B being a second probe which has a sequence S' complementary to a second partial sequence S of the target nucleic acid and a flag bound to the sequence S', where said flag is a double-stranded sequence and has a marker substance in one of the double strand;

(b) hybridizing the first probe A with the first partial sequence F of the target nucleic acid and hybridizing the second probe B with the second partial sequence S of the target nucleic acid;

(c) ligating the first probe A and the second probe B both being hybridized with the target nucleic acid, thereby obtaining a probe (A+B);

(d) binding the binding molecule to a substance which is paired up therewith, thereby recovering the probe (A+B); and

(e) recovering a single-stranded nucleic acid having the marker substance of the double stranded nucleic acid constituting the flag and detecting or quantifying the marker substance, thereby detecting or quantifying the target nucleic acid in the specimen.

2.(Amended) A method of detecting or quantifying target nucleic acids N1-Nn (n is an integer of 2 or more), each having a predetermined sequence, in a specimen, comprising:

(a) preparing probes A1-An (n is an integer of 2 or more) and probes B1-Bn (n is an integer of 2 or more),

said probes A1-An being first probes which respectively have sequences F1'-Fn' (n is an integer of 2 or more) complementary to first partial sequences F1-Fn (n is an integer of 2 or more) of the target nucleic acids and a binding molecule bound to each of the sequences F1'-Fn', and

said probes B1-Bn (n is an integer of 2 or more) being second probes which respectively have sequences S1'-Sn' (n is an integer of 2 or more) complementary to second partial sequences S1-Sn (n is an integer of 2 or more) of the target nucleic acids and flags bound to the sequences S1'-Sn', where each of said flags is a double-stranded sequence and has a marker substance in one of the double strand; and

G1 cont.

(b) respectively hybridizing the first probes A1-An with the first partial sequence F1-Fn of the target nucleic acids, and simultaneously hybridizing the second probes B1-Bn with the second partial sequences S1-Sn of the target nucleic acids, respectively;

(c) respectively ligating the first probes A1-An and the second probes B1-Bn, both being hybridized with the target nucleic acids, respectively, thereby obtaining probes (A1+B1)-(An+Bn) (n is an integer of 2 or more);

(d) binding the binding molecule to a substance which is paired up therewith, thereby recovering the probes (A1+B1)-(An+Bn); and

(e) recovering a single-stranded nucleic acid having the marker substance from the double-stranded nucleic acid constituting each of the flags and detecting or quantifying the marker substance, thereby detecting or quantifying each of the target nucleic acids N1-Nn in the specimen.

8.(Amended) A method of detecting or quantifying a target nucleic acid having a predetermined sequence in a specimen comprising:

(a) preparing a probe A and a probe B,

said probe A being a first probe which has a sequence F' complementary to a first partial sequence F of the target nucleic acid and a binding molecule bound to the sequence F', and

said probe B being a second probe which has a sequence S' complementary to a second partial sequence S of the target nucleic acid and a flag sequence FL consisting of 4 units bound to the sequence S', where said flag FL sequence hybridizes with a sequence FL' bound to the sequence S' to form a double-stranded sequence; and

(b) mixing the probe A, probe B and the specimen, thereby hybridizing the probe A with the first partial sequence F of the target nucleic acid, and simultaneously hybridizing the second probe B with the second partial sequence S of the target nucleic acid;

(c) ligating the probe A and the probe B, both being hybridized with the target nucleic acid, thereby obtaining a probe (A+B);

(d) binding the binding molecule to a substance which is paired up therewith, thereby recovering the probe (A+B); and

(e) denaturing the double-stranded flag sequence of the probes (A+B) recovered into single-stranded flag sequence;

(f) hybridizing the single-stranded flag sequence with two primers one of which has a binding molecule B and the other of which has a marker substance L, and extending the primers to form a complementary strand of the flag sequence FL, thereby obtaining a double strand;

(g) binding a binding molecule B with a substance capable of being paired with the binding molecule B, thereby recovering the double strand; and

(h) detecting or quantifying the target substance L, thereby detecting or quantifying the target nucleic acid in the specimen.

B2 cont.

9.(Amended) A method of detecting or quantifying target nucleic acids N1-Nn (n is an integer of 2 or more), each having a predetermined sequence, in a specimen, comprising:

(a) preparing probes A1-An (n is an integer of 2 or more) and probes B1-Bn (n is an integer of 2 or more),

said probes A1-An being first probes which respectively have sequences F1'-Fn' (n is an integer of 2 or more) complementary to first partial sequences F1-Fn (n is an integer of 2 or more) of the target nucleic acids and a binding molecule bound to each of the sequences F1'-Fn', and

said probes B1-Bn (n is an integer of 2 or more) being second probes which respectively have sequences S1-Sn' (n is an integer of 2 or more) complementary to second partial sequences S1-Sn (n is an integer of 2 or more) of the target nucleic acids, and flag sequences FL1-FLn each consisting of 4 units, bound to the sequences S1'-Sn', where said flag sequences FL1-FLn hybridize respectively with sequences FL1'-FLn' bound to the sequences S1'-Sn' to form double-stranded sequences; and

(b) mixing the probes A1-An, the probes B1-Bn, and the specimen, thereby hybridizing probes A1-An respectively with the first partial sequences F1-Fn of the target nucleic acids N1-Nn, and simultaneously hybridizing the probes B1-Bn with the second partial sequences S1-Sn of the target nucleic acids N1-Nn;

(c) respectively ligating the probes A1-An and the probes B1-Bn, both being hybridized with the target nucleic acids N1-Nn, thereby obtaining probes (A1+B1)-(An+Bn);

(d) binding each of the binding molecules to a substance which is paired up therewith, thereby recovering the probes (A1+B1)-(An+Bn); and

(e) denaturing the double-stranded flag sequences of the probes (A1+B1)-(An+Bn) recovered into single-stranded flag sequences;

B2 cont.

(f) hybridizing the single-stranded flag sequences FL1-FLn with two primers one of which has a binding molecule B and the other of which has a marker substance L, and extending the two primers, to form complementary strands of the flag sequences FL1-FLn, thereby obtaining double strands;

(g) binding a binding molecule B with a substance capable of being paired therewith, thereby recovering the double strands; and

(h) detecting or quantifying the marker substance L, thereby detecting or quantifying the target nucleic acids N1-Nn in the specimen.

10.(Amended) A method of detecting or quantifying a target nucleic acid having a predetermined sequence in a specimen comprising:

(a) preparing a probe A and a probe B,

said probe A being a first probe which has a sequence F' complementary to a first partial sequence F of the target nucleic acid and a binding molecule bound to the sequence F', and

said probe B being a second probe which has a sequence S' complementary to a second partial sequence S of the target nucleic acid and a flag consisting of 4 units bound to the sequence S', where said flag FL is a double-stranded sequence; and

(b) mixing the probe A, the probe B, and the specimen, thereby hybridizing the probe A with the first partial sequence F of the target nucleic acid and simultaneously hybridizing the probe B with the second partial sequence S of the target nucleic acid;

(c) ligating the probe A and the probe B, both being hybridized with the target nucleic acid, thereby obtaining a probe (A+B);

(d) binding the binding molecule to a substance which is paired up therewith, thereby recovering the probe (A+B); and

(e) denaturing the double-stranded nucleic acid constituting the flag into single-stranded nucleic acid;

(f) amplifying the single-stranded nucleic acid present in a liquid phase by PCR, thereby performing an encode reaction;

(g) performing transcription of a sequence FL' complementary to the single stranded flag sequence obtained by the encode reaction, by use of two primers one of which is a primer having another binding molecule and the other of which is a primer having a marker substance, thereby performing a decode reaction;

(h) binding said another binding molecule to a substance being paired up therewith, recovering a nucleic acid molecule obtained by the decode reaction; and

(i) detecting or quantifying the marker substance, thereby detecting or quantifying the target nucleic acid.

11.(Amended) A method of detecting or quantifying target nucleic acids N1-Nn (n is an integer of 2 or more), each having a predetermined sequence, in a specimen, comprising:

(a) preparing probes A1-An (n is an integer of 2 or more) and probes B1-Bn (n is an integer of 2 or more),

said probes A1-An being first probes which respectively have sequences F1'-Fn' (n is an integer of 2 or more) complementary to first partial sequences F1-Fn (n is an integer of 2 or more) of the target nucleic acids and a binding molecule bound to each of the sequences F1'-Fn', and

said probes B1-Bn (n is an integer of 2 or more) being second probes which respectively have sequences S1'-Sn' (n is an integer of 2 or more) complementary to second partial sequences S1-Sn (n is an integer of 2 or more) of the target nucleic acids and flag sequences FL1-FLn each consisting of 4 units, bound to the sequences S1'-Sn';

(b) mixing the first probes A1-An, the second probes B1-Bn, and the specimen, thereby hybridizing the probes A1-An respectively with the first partial sequences F1-Fn of the target nucleic acids N1-Nn and simultaneously hybridizing the probes B1-Bn with the second partial sequences S1-Sn of the target nucleic acids N1-Nn, respectively;

(c) respectively ligating the probes A1-An and the probes B1-Bn, both being hybridized with the target nucleic acids N1-Nn, thereby obtaining probes (A1+B1)-(An+Bn) (n is an integer of 2 or more);

(d) binding the binding molecule to a substance which is paired up therewith, to recover the probes (A1+B1)-(An+Bn), and thereafter performing an encode reaction of each of the flags FL1-FLn; and

(e) performing a decode reaction of the sequences FL1'-FLn' complementary to the flags FL1-FLn obtained by the encode reaction; and

(f) detecting or quantifying the nucleic acid molecules obtained by the decode reaction, thereby detecting or quantifying the target nucleic acids N1-Nn in the specimen.

12.(Amended) A method of detecting or quantifying target nucleic acids N1-Nn (n is an integer of 2 or more), each having a predetermined sequence, in a specimen, comprising:

(a) preparing probes A1-An (n is an integer of 2 or more) and probes B1-Bn (n is an integer of 2 or more),

B2 cont.

said probes A1-An being first probes which respectively have sequences F1'-Fn' (n is an integer of 2 or more) complementary to first partial sequences F1-Fn (n is an integer of 2 or more) of the target nucleic acids and a binding molecule bound to each of the sequences F1'-Fn', and

said probes B1-Bn (n is an integer of 2 or more) being second probes which respectively have sequences S1'-Sn' (n is an integer of 2 or more) complementary to second partial sequences S1-Sn (n is an integer of 2 or more) of the target nucleic acids and flag sequences FL1-FLn each consisting of 4 units, bound to the sequences S1'-Sn', respectively,

(b) mixing the probes A1-An, the probes B1-Bn, and the specimen, thereby hybridizing probes A1-An respectively with the first partial sequences F1-Fn of the target nucleic acids N1-Nn, and simultaneously hybridizing the probes B1-Bn with the second partial sequences S1-Sn of the target nucleic acids N1-Nn, respectively;

(c) respectively ligating the probes A1-An and the probes B1-Bn, both being hybridized with the target nucleic acids N1-Nn, thereby obtaining probes (A1+B1)-(An+Bn);

(d) binding each of the binding molecules to a substance which is paired up therewith to recover the probes (A1+B1)-(An+Bn), and thereafter performing an encode reaction for each of the flags FL1-FLn; and

(e) performing a decode reaction of the sequences F11'-FLn' complementary to the flags FL1-FLn (n is an integer of 2 or more) obtained by the encode reaction; and

(h) detecting the nucleic acid molecules obtained by the decode reaction, thereby detecting or quantifying the target nucleic acids N1-Nn in the specimen,

wherein 2 units of 4 units are sequences functioning as primers for PCR amplification.

B2 cont

13.(Amended) A method of detecting or quantifying a target nucleic acid having a predetermined sequence in a specimen comprising:

(a) preparing a probe A and a probe B, said probe A being a first probe which has a sequence F' complementary to a first partial sequence F of the target nucleic acid and a binding molecule bound to the sequence F', and

said probe B being a second probe which has a sequence S' complementary to a second partial sequence S of the target nucleic acid and a flag consisting of 4 units bound to the sequence S1, where said flag FL is a double-stranded sequence and said 4 units consist of SD, D0, D1 and ED each having an arbitrary sequence, bound to each other sequentially in the order mentioned; and

(b) mixing the probe A, the probe B, and the specimen, thereby hybridizing the probe A with the first partial sequence F of the target nucleic acid and simultaneously hybridizing the probe B with the second partial sequence S of the target nucleic acid;

(c) ligating the probe A and the probe B both being hybridized with the target nucleic acid, thereby obtaining a probe (A+B);

(d) binding the binding molecule to a substance which is paired up therewith, thereby recovering the probe (A+B); and

(e) denaturing the double-stranded nucleic acid constituting the flag into a single-stranded nucleic acid;

(f) hybridizing the single-stranded nucleic acid obtained in a liquid phase with sequences complementary to sequences D11-D1n labeled with a marker substance, as primers,

(g) extending the primers hybridized

(h) denaturing a double-stranded nucleic acid having primers into a single-stranded nucleic acid;

(i) hybridizing the sequences D01-D0n specifically with the primers extended to detect or quantify the marker substances included in the sequences D01-D0n, thereby detecting or quantifying the target nucleic acids.

14.(Amended) The method according to claims 10 to 12, wherein the decode reaction comprises, where said flag(s) FL is a double-stranded sequence and said 4 units consist of SD, D0, D1 and ED each having an arbitrary sequence, bound to each other sequentially in the order mentioned,

(i) performing PCR for a single-strand sequence encoded using SD sequence to which a binding molecule is attached, and ED sequence, as primers;

(ii) binding a binding molecule bound to the SD sequence to a substance which is paired up therewith, thereby recovering a PCR product;

(iii) denaturing the PCR produce into a single strand

(iv) hybridizing the single strand with primers D11'-D1n' labeled;

(v) extending the primers'

(vi) denaturing the primers extended into single strands;

(vii) hybridizing extended single strands of the primers with sequences D01-D0n to detect or quantify marker substances included in that sequences D01-D0n, thereby detecting or quantifying the target nucleic acid.

15.(Amended) The method according to claims 10 to 12, wherein the decode reaction comprises, where said flag FL is a double-stranded sequence and said 4 units consist of SD, D0, D1 and ED each having an arbitrary sequence, bound to each other sequentially in the order mentioned; and

(i) performing PCR for a single-stranded sequence encoded using SD sequence to which a binding molecule is attached and ED sequence, as primers;

(ii) binding the binding molecule bound to the SD sequence to a substance which is paired up therewith, thereby recovering a PCR product;

(iii) denaturing the PCR product into a single strand;

(iv) mixing the sequences D1n' labeled and D0n' labeled, thereby hybridizing the single strand with the sequences D1n' and D0n';

(v) denaturing the sequences ligated into a single-stranded sequence;

(vii) hybridizing sequences D01-D0n with the single-stranded sequence labeled with a marker substance, to detect or quantify the marker substance, thereby detecting or quantifying the target nucleic acid.

REMARKS

In the Official Action dated April 19, 2002, claims 1, 2 and 8-16 have been rejected under 35 U.S.C. §112, second paragraph as allegedly indefinite. Claims 1-2 and 13-16 have been rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Carr, European

Patent Application No. 0 246 864, May 19, 1987 (hereinafter "Carr") in view of Cantor et al., U.S. Patent No. 6,007,987 (hereinafter "Cantor et al."). Claims 1-9 and 13-16 have been rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Carr in view of Cantor et al. and further in view of Wong, U.S. Patent No. 5,935,793 (hereinafter "Wong"). Claims 1-2 and 10-16 have been rejected under 35 U.S.C. §103(a) over Carr in view of Cantor et al. and further in view of Cleuziat et al., U.S. Patent No. 6,218,151 (hereinafter "Cleuziat et al.").

This response addresses each of the Examiner's rejections. Accordingly, the present application is in condition for allowance. Favorable consideration of all pending claims is therefore respectfully requested.

Claims 1, 2 and 8-16 have been rejected under 35 U.S.C.§112, second paragraph as allegedly indefinite. The Examiner alleges that the phrase "capable of being" in claims 1, 2 and 8-16 is allegedly unclear. In response, and in an effort to expedite favorable prosecution, Applicants have substituted the phrase "capable of being" from claims 1, 2 and 8-16 with a clarifying phrase "which is". No new matter has been added.

Claims 1-2 and 8-13 have been rejected as allegedly unclear in view of the phrase "binding the binding molecule". In response, Applicants respectfully submit that the object to which "binding molecule" binds is the "substance which is paired up therewith". In other words, there is a binding relationship between the before-mentioned materials, that is, one of the components that makes up the "binding pair" is the "binding molecule" and the other component is the "substance". The specification provides ample description for this relationship at, for example, page 10, line 20 to page 11, line 10.

Claims 13-16 have also been rejected based on the recitation "bounded" in claim 13. In response, Applicants have amended claim 13 to recite "bound". The Examiner

also rejects claims 13-16 because certain units called "SD, D0, D1 and ED" are allegedly unclear. Applicants respectfully direct the Examiner's attention to the "example of detection method" provided at pages 34-43 which provides a clear description of a plurality of units contained in a flag FL containing "SD". Furthermore, it is respectfully submitted that the skilled artisan understands that "SD" in the context of the description of the present invention does not denote "standard error" or "standard deviation". Furthermore, according to the specification at page 5, line 15 to page 6, line 24, the skilled artisan recognizes that the sequence of the units "SD, D0, D1 and D2" can be designed arbitrarily by the practitioner in advance. This feature is advantageous when a target specific sequence is to be encoded in accordance with a combination of sequences of "SD, D0, D1 and ED", in advance.

Accordingly, the rejection of claims 1-2 and 8-13 under 35 U.S.C. §112, second paragraph and withdrawal thereof is respectfully requested.

Claims 1-2 and 13-16 have been rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Carr in view of Cantor et al. The Examiner alleges that Carr teaches a method of detecting or quantifying a target nucleic acid having a predetermined sequence in a specimen in accordance with the method steps of claims 1 and 2. The Examiner concedes that Carr does not teach a probe with a double-stranded flag containing 4 units consisting of SD, D0, D1 and ED, each having an arbitrary sequence bound to each other sequentially and a marker substance. The Examiner further concedes that Carr does not teach the multiplexing step or quantifying step. The Examiner applies Cantor et al. in an effort to ameliorate the admitted deficiencies of Carr. The Examiner alleges that "by employing scientific reasoning, an ordinary artisan would have substituted and combined a probe with a double-stranded flag containing 4 units consisting of SD, D0, D1 and ED and the multiplexing of detecting or

quantifying a target nucleic acid having a predetermined sequence in a specimen with multiple probes A1-An and B1-Bn of Cantor et al. in order to improve the detection and identification of multiple target nucleic acids". The Examiner further alleges that the ordinary artisan would have been motivated to combine and substitute a probe with a double-stranded flag containing 4 units consisting of SD, D0, D1 and ED and the multiplexing of detecting or quantifying a target nucleic acid...in order to achieve the express advantages noted by Cantor of the structure of probes which provides hybridization of the target nucleic acid".

Applicants respectfully submit that the cited references fail to teach or suggest the invention, as claimed. Applicants submit that the Examiner has asserted an improper basis for rejecting the claims in view of Carr and Cantor. Specifically, a rejection under 35 U.S.C. §103 requires a suggestion or motivation to make or use the claimed invention must be found in the references themselves, not as a consequence of deduction or scientific reasoning. Scientific reasoning is effectively hindsight reconstruction of the invention which is not permitted. Furthermore, the asserted combination fails inasmuch as Carr does not disclose a double-stranded flag of a probe DNA of the present invention. Furthermore, only one type of probe is employed by Carr in one reaction system. The Carr method is incapable of detecting a target nucleic acid in a multiplex manner. Cantor et al. do not bridge the gaps which are admittedly present in the Carr reference. Specifically, Cantor et al. do not disclose or even suggest a double-stranded flag containing 4 units, an aspect of the claimed invention. According to Cantor et al. while manufacturing a nucleic acid array, a nucleic acid on the array is elongated by an enzyme or nucleic acids are synthesized into a nucleic acid strain. In this manner, after fixation of the nucleic acid to a solid support, the nucleic acid configuration varies. Cantor et al. disclose a probe that partially contains a single strand and is fixed to an

array. Cantor et al. further disclose a method of hybridizing and ligating a target strain of an unknown sequence with part of a single strain of the probe and digesting it with a restriction enzyme. Cantor et al. require the preparation of a great number of sequences prior to detection. Cantor et al. thus represents a clear teaching away from the present invention which detects unknown nucleic acid specimens contained in a sample by copying and replacing the information of a nucleic acid to be detected on a flag sequence, in one embodiment. Furthermore, according to the Cantor et al. reference, a ligation reaction as carried out between a probe nucleic acid fixed to a solid support and a target nucleic acid. In contrast, in the examples of the present invention, ligation is carried out between first and second probes. Moreover, the ligation step of the present invention can be carried out in a liquid phase and at greater efficiency then that disclosed by Cantor et al. Accordingly, the rejection of claims 1-2 and 13-16 under 35 U.S.C. §103(a) is overcome and withdrawal thereof is respectfully requested.

Claims 1-9 and 13-16 have been rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Carr in view of Cantor and in further view of Wong. The teachings of Carr and Cantor et al. are fully discussed above. The Examiner concedes that Carr in view of Cantor et al. do not teach the hybridization of the tag sequence Tg with a complementary sequence Tg' to recover the probes. The Examiner alleges that Wong teaches the hybridization of Tg sequence with a complementary sequence Tg' and that by employing "scientific reasoning an ordinary artisan would have substituted and combined the hybridization of the tag sequence Tg with a complementary sequence tag Tg' of Wong into the method of detecting or quantifying a target nucleic acid having a predetermined sequence in a specimen of Carr in view of Cantor et al. in order to improve the detection and

identification of multiple target nucleic acids". The Examiner further alleges that the skilled artisan would have been motivated to combine and substitute the teachings of Wong into the method of Carr in view of Cantor et al. "in order to achieve the express advantages noted by Wong of a method that results in an increased quantity of identifier tag with a relative reduction in sample-derived background" to increase sensitivity for detecting the identifier tag on a probe-array. Applicants submit that the Examiner has used the aid impermissible hindsight in evaluating the claimed invention. Applicants submit that there is no motivation to combine Carr, Cantor et al. and Wong, within the respective cited references. According to the technique disclosed in Wong, the skilled artisan does not determine in advance which tag corresponds to which gene. In other words, Wong et al. fail to recognize a relationship between the sequence inserted into a vector and the detection of a tag sequence. Notably, in the method of the present invention, a tag (flag) sequence and a sequence of nucleic acids to be detected are designed to correspond with each other, one by one, in advance. Moreover, according to Wong it is necessary to provide a step of identifying the sequence of the tag molecule by its length, whereas the present invention requires no step of distinguishing tags by lengths, such as by electrophoresis.

Accordingly, the rejection of claims 1-9 and 13-16 under 35 U.S.C. §103(a) is overcome and withdrawal thereof is respectfully requested.

Claims 1-2 and 10-16 have been rejected under 35 U.S.C. §103(a) over Carr in view of Cantor et al. and further in view of Cleuziat et al. The teachings of Carr and Cantor are fully distinguished above. By admission, the Examiner states that Carr in view of Cantor et al. do not teach the sequencing by transcription of a single-stranded nucleic acid by the use of two primers. Again, the Examiner attempts to remedy this fault in the combination of Carr

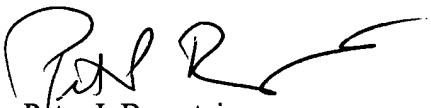
and Cantor by applying Cleuziat et al. and "scientific reasoning" to arrive at the claimed invention. Again, this is impermissible and fails to establish a *prima facie* basis for a rejection under 35 U.S.C. §103(a). Notably, Cleuziat et al. do not disclose or even suggest the claimed technique. The method of Cleuziat et al., as illustrated in figures 1 and 13 is directed to elongating two complementary strands at the same time from one DNA or one RNA by double-elongating two primers in the same direction. The present invention is directed to a method of detecting or quantifying a target nucleic acid without the need of primer double-elongation.

Accordingly, the rejection of claims 1-2 and 10-16 under 35 U.S.C. §103(a) is overcome and withdrawal thereof is respectfully requested.

Attached hereto is a marked up version of the changes made to the claims by the current amendment. The attached page is captioned **"Version with Markings to Show Changes Made."**

Accordingly, the present invention is in condition for allowance, which action is earnestly solicited.

Respectfully submitted,



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